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IMPLANTABLE DEFIBRILLATOR AT END OF LIFE WITH EMPHASIS ON DEACTIVATION AND GUIDELINE COMPLIANCE

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Printed by E-Print
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ISBN 978-91-7676-268-4

IMPLANTABLE DEFIBRILLATOR AT END OF LIFE – WITH EMPHASIS ON DEACTIVATION AND GUIDELINE COMPLIANCE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Oroas ej. Räds ej i uppbrottstimman.

En vänlig hand lugnt ordnar

båtens segel,

som för dig bort från

kvällens land till dagens.

Gå utan ängslan ner

i strandens tystnad,

den mjuka stigen genom

skymningsgräset.

Pär Lagerkvist

ABSTRACT

Introduction

Implantable Cardioverter Defibrillators (ICD) have been demonstrated to improve survival in cardiac patients with high risk for sudden death. The incidence of ICD implantations is increasing worldwide. The cause and nature of death in the ICD population has been insufficiently investigated. In 2010 consensus statements were published to address and highlight the management of ICD patients who were nearing end of life. The overall aim of this thesis was to study patients with implantable defibrillator in end of life as well as physicians' knowledge about ICD treatment and compliance to guidelines concerning ICD management.

Methods and Results

Study I: An observational study exploring intracardiac electrograms from 125 deceased ICD patients. Ventricular tachyarrhythmia occurred in 35% of those patients during the last hour of their lives, and 31% received shock treatment during the last 24 hours. 52% of the patients had a do-not-resuscitate (DNR) order, but still had shock therapy active 24 hours before death in 65% of cases.

Study II: An observational analysis of 65 deceased ICD patients with DNR order. The majority (86%) of patients were treated in hospitals, mainly (63%) in university hospitals and (33%) in Cardiology wards. Patients had active ICD therapy in 51% of cases despite a DNR order, and 24% of those patients experienced shocks as consequence. Patients with active ICD therapy had a median of 4 days (IQR 1-38) from decision of DNR to death. In the 38% of the patients who had ICD therapy deactivated, the deactivation was performed two days or more after the DNR decision.

Study III: A cross-sectional comparative study with development of a questionnaire that was distributed among 432 physicians in 14 hospitals with a response rate of 99.5%. Many (83%) of the physicians said they had experience with ICD patients and 68% of physicians rated their ICD knowledge to be low. Sufficient knowledge regarding ICD therapy defined according to pre-specified criteria was observed in 41%. Physicians in Cardiology departments scored significantly higher than others. Only 30% of physicians in Internal Medicine and 19% of physicians in Geriatrics reached sufficient knowledge compared with 71% in Cardiology.

Study IV: A comparison of two cohorts of ICD patients who died in hospitals before and after the implementation of new guidelines. Almost two-thirds of ICD patients in the two groups died in wards other than Cardiology. In group 1 patients had a DNR order in 54% compared to 73% in group 2. Shock deactivation was present in 52% of the patients in group 1 compared to 67% in group 2. The difference in deactivation rate between group 1 and 2 was

only significant (p=0.016) for DNR patients treated in Cardiology. A significant difference (p=0.038) was also found in deactivation within group 2 between DNR patients treated in Cardiology vs. DNR patients in Non-Cardiology.

Conclusions

Patients with ICD dies in hospitals and the majority are treated in Non-Cardiology wards. Approximately one-third of patients with an ICD have ventricular tachyarrhythmia at end of life. Many patients have a DNR order but still have shock therapy active and thus receive unnecessary shocks before death. Deactivation rates have increased but not significantly since publications of international guidelines on the management of ICD in patients at end of life. Physicians in Cardiology, Internal Medicine, and Geriatrics have a lack of basic ICD knowledge, possibly affecting their ability to manage ICD patients and may increase the risk for unnecessary suffering for these patients at end of life.

LIST OF SCIENTIFIC PAPERS

I. Kinch Westerdahl A, Sjöblom J, Mattiasson A-C, Rosenqvist M, Frykman V. Implantable cardioverter-defibrillator therapy before death: high risk for painful shocks at end of life.
Circulation. 2014;129(4):422-9

II. Kinch Westerdahl A, Sutton R, Frykman V. Defibrillator patients should not be denied a peaceful death.
International Journal of Cardiology. 2015;182:440-6

III. Kinch Westerdahl A, Frykman V. Physicians' knowledge of implantable defibrillator treatment. Are we good enough?
Submitted

IV. Kinch Westerdahl A, Magnsjö J, Frykman V. Deactivation of implantable defibrillators at end of life- can we do better?
Manuscript

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LIST OF ABBREVIATIONS

AD	Advance directive
ANOVA	Analysis of Variance
ATP	Anti tachycardia Pacing
CAD	Coronary Artery Diseases
CPR	Cardiopulmonary Resuscitation
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Defibrillator
EF	Ejection Fraction
EGM	Intracardiac Electrograms
EOL	End of Life
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IQR	Interquartile Range
NYHA	New York Heart Association
SCD	Sudden Cardiac Death
SD	Standard Deviation
S-ICD	Subcutaneous Implantable Defibrillator
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WHO	World Health Organization
QOL	Quality of Life

1 INTRODUCTION

1.1 SUDDEN CARDIAC DEATH

Cardiovascular diseases are the number one cause of death throughout the world and are responsible for approximately 17 million deaths per year. About 25% of these deaths are caused by sudden cardiac death (SCD) [1-3]. The risk of SCD is higher in men than in women and increases with age. This is due to a higher prevalence of Coronary Artery Disease (CAD) in older people as well as other chronic heart diseases such as heart failure [4]. In young people, channelopathies, cardiomyopathy and myocarditis are the most common causes of SCD [5].

Sudden cardiac death is often caused by a life-threatening arrhythmia such as ventricular tachycardia (VT) or ventricular fibrillation (VF), conditions with rapid and uncoordinated contractions of ventricles of the heart that make it quiver rather than contract properly. The arrhythmia will result in SCD within minutes if not treated. The only way to convert VF is to deliver an electrical shock from a defibrillator, externally or internally i.e. with an implantable defibrillator (Figure 1).

Figure 1. Historical development of the ICD. Image provided courtesy of Boston Scientific. © 2016 Boston Scientific Corporation or its affiliates. All rights reserved.

1.2 IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

The Implantable Cardioverter Defibrillator (ICD) was invented by Dr. M. Mirowski and implanted in humans for the first time in 1980. He was inspired to develop the ICD after one of his colleague suffered from episodes of VT and later died of SCD [6]. Since then several studies have demonstrated improved survival with ICD therapy for selected patient groups [7, 8]. During the past decade, the indication for such therapy has evolved. Today ICD are offered as secondary prevention to patients who have survived a prior cardiac arrest or sustained VT. In recent years ICD are also offered as primary prevention to individuals

without a history of cardiac arrest but with an increased risk of developing life-threatening ventricular arrhythmias in the future [9-12]. The Swedish National Board of Health has given primary prevention the same level (level 2 on a scale 1-10) of recommendation as secondary prevention [13].

The number of patients who meet the guideline-recommended indications for ICD treatment is increasing. The majority of patients today receive their ICD as primary prevention. The exact number of active devices in the world is unknown, but recent surveys have reported over 130,000 implantations per year in the USA and 70,000-80,000 in Europe [14, 15]. There is a large variation in implantation rates in Europe. The number of ICD implantations per million inhabitants in 2013 was more than twice as high in Western Europe than in other countries in Eastern Europe due to socio-economical factors (Figure 2) [16]. In 2014 there were over 9,000 active ICD patients in Sweden. Sixty-eight percent of all new implants were due to primary prevention [17].

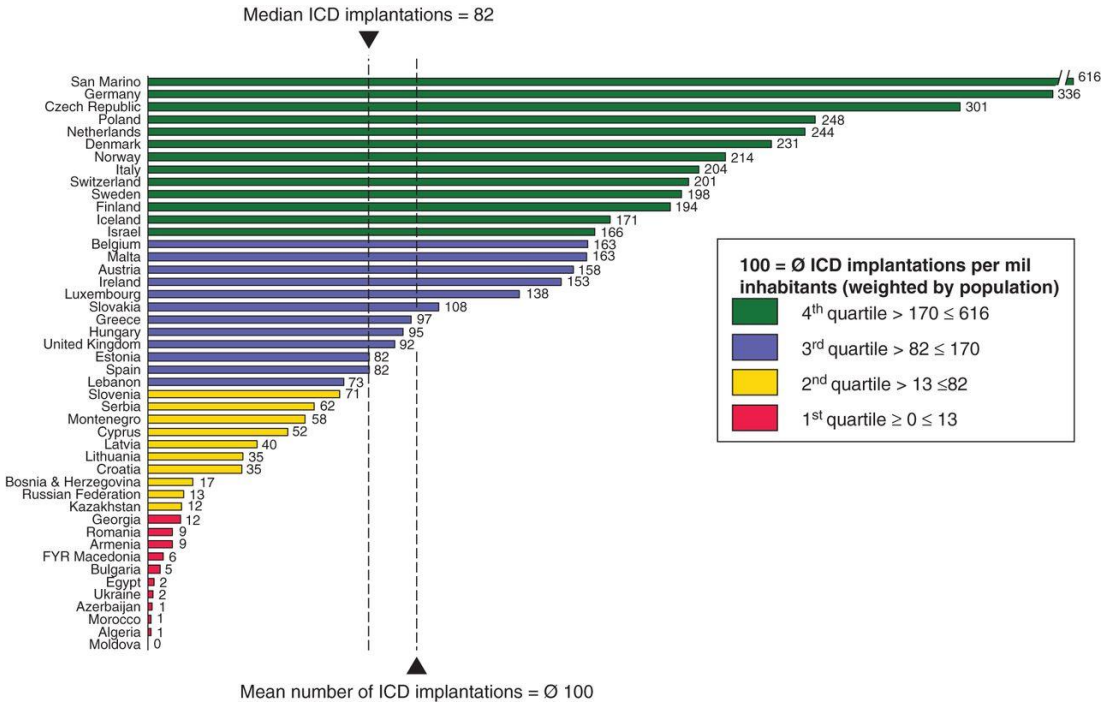

Figure 2. Implantable Cardioverter Defibrillator (ICD) implantations per million inhabitants in 2013. Reproduced from Europace, Raatikainen MJ et al, 2015, 17, i1-75, by permission of Oxford University Press.

Initially the ICD was implanted surgically in the abdomen and connected to leads fixed to the ventricles via thoracotomy. This was a complex procedure with long hospitalization and convalescence for the patient. The first ICD had shock as the only therapy option. The transvenous approach is now the standard implantation routine and has been for many years. One, two or three electrodes are placed trough a vein into the right chambers of the heart. In the cases were only one electrode is used, the electrode is inserted in to the right ventricle. That system is called single-chamber ICD. Most patients receive a dual-chamber ICD where a second lead is inserted to the right atrium (Figure 3). Sometimes patients with heart failure and broad QRS may receive an additional left ventricular electrode placed

through the coronary sinus into a vein on the left side of the heart. The two ventricular electrodes will, by pacing, resynchronize the contractions of the heart's ventricles. The system is called Cardiac Resynchronization Therapy (CRT), and it can be used in combination with a defibrillator (CRT-D) [18].

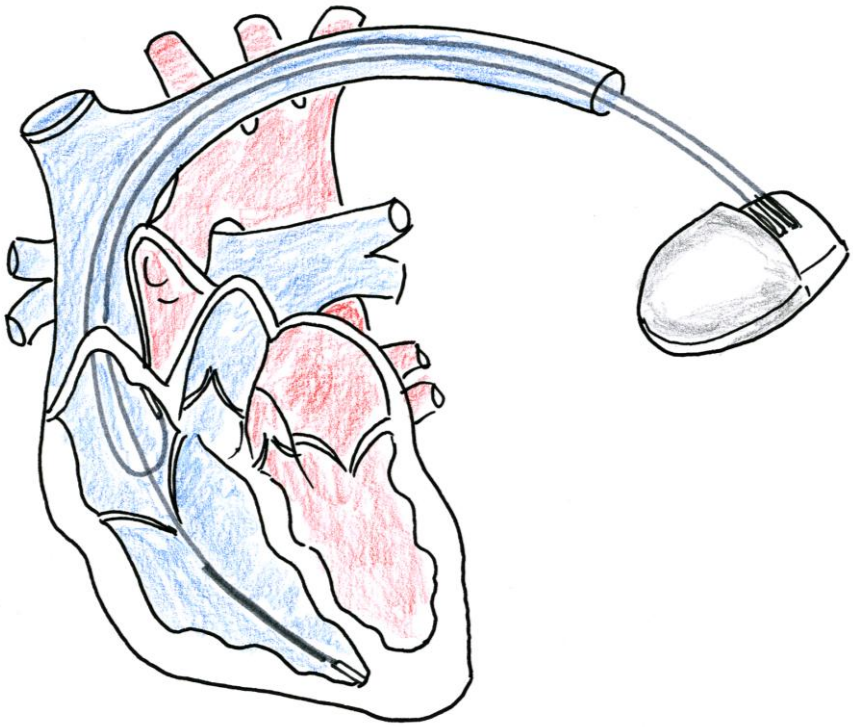

Figure 3. Implanted ICD system with one atrial electrode and one high-voltage electrode in the right ventricle (illustration by Marianne Westerdahl).

Recently, a subcutaneous ICD (S-ICD) has been introduced where the pulse generator is implanted on the left side of the patient's thorax, below the axillary, and connected to a single lead which is tunneled under the skin (Figure 4). Compared to the ordinary ICD, the S-ICD cannot pace and is therefore not appropriate for patients with bradycardia or when CRT is considered [19].

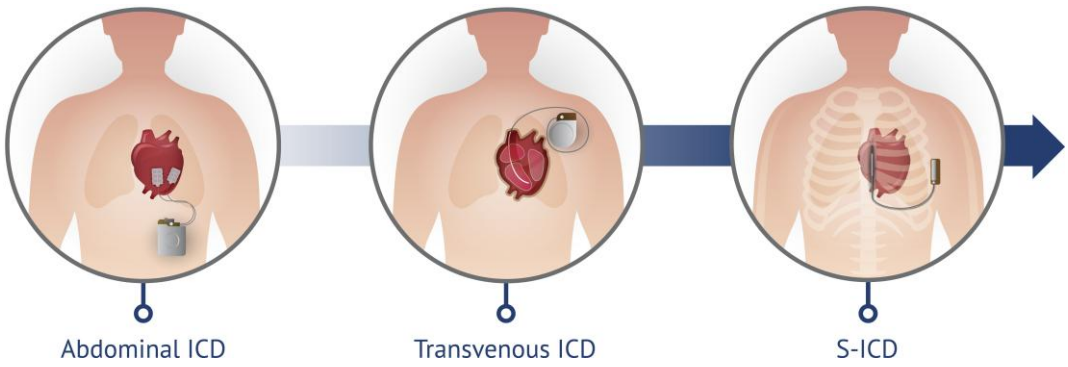

Figure 4. From abdominal implant, transvenous and subcutaneous ICD. Image provided courtesy of Boston Scientific. © 2016 Boston Scientific Corporation or its affiliates. All rights reserved.

1.3 ICD THERAPY

The ICD monitors the heart rhythm continuously. If a life-threatening arrhythmia occurs, the ICD promptly identifies it and treats it appropriately according to the ICD's programming. Programming is done within specific VT or VF zones defined by the heart rate. The ICD will start to identify and, if appropriate, deliver therapy if the arrhythmia is above the programmed heart rate. If the arrhythmia is identified as a VT, the ICD is usually programmed to terminate the arrhythmia with anti-tachypacing (ATP) as the first line of treatment. The ATP is a number of pacing stimuli given at a faster rate than the arrhythmia itself [18].

If the ICD identifies the arrhythmia as a VF, or if it is not successful in terminating the arrhythmia with ATP, it will deliver a high-voltage electrical shock in the region of 30-40 Joules (500-800 Volts) (Figure 5). Shock treatment is administered through defibrillator coils on the electrode and the can of the ICD [18]. The ICD will continue to deliver consecutive shocks either until the arrhythmia is terminated or until the maximum number of shocks for the device has been reached which is up to 6-8 shocks depending on manufacturer. Sometimes the arrhythmia starts over again. This is called an arrhythmic storm. In these cases, the device can deliver shocks until the battery is completed which could result in up to 100-200 shocks. When suffering from an arrhythmic storm the patient needs acute medical attention. Patients are instructed to seek medical advice when they suffer from a shock to avoid the scenario with multiple shocks [20].

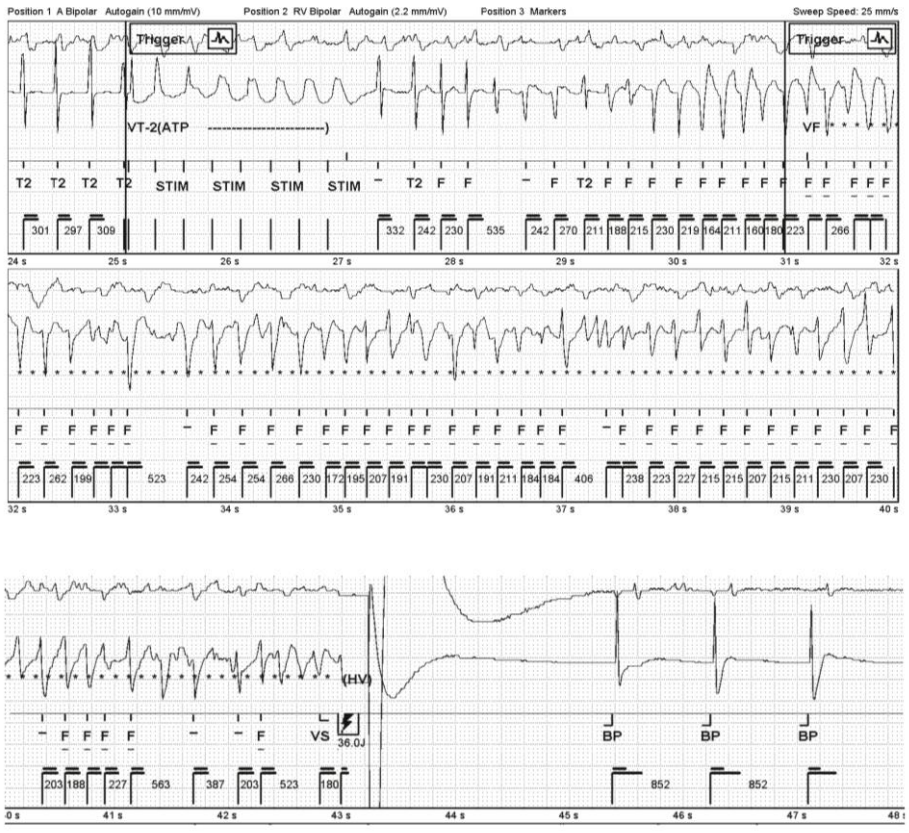

Figure 5. Patient with ICD in end of life with ventricular arrhythmia treated with ATP and shock therapy.

1.4 COMPLICATIONS

Appropriate shock therapy – which is lifesaving in many cases – has an annual rate of 6.0-7.5% [9, 21]. ICD therapy is generally well-accepted by patients and is associated with preserved or improved quality of life when compared with anti-arrhythmic medical treatment [22-24]. However, shock treatment may also lead to distress and sometimes problems with device acceptance (Figure 6) [25].

Patients have described ICD shocks as "being hit by a truck," or "being kicked by a horse" and on average have rated them a 6 on a 0-10 pain scale [26]. Shocks are painful and can cause anxiety [22, 27, 28]. Studies have shown a lower health-related quality of life (QOL) for patients who receive shocks, compared with those who do not [22-24, 29]. Anxiety (8-63%) as well as depression (5-41%) are common psychological complications where the occurrence of shocks, especially inappropriate shocks, is a risk factor for feeling distressed [20, 22, 23, 28, 30-35].

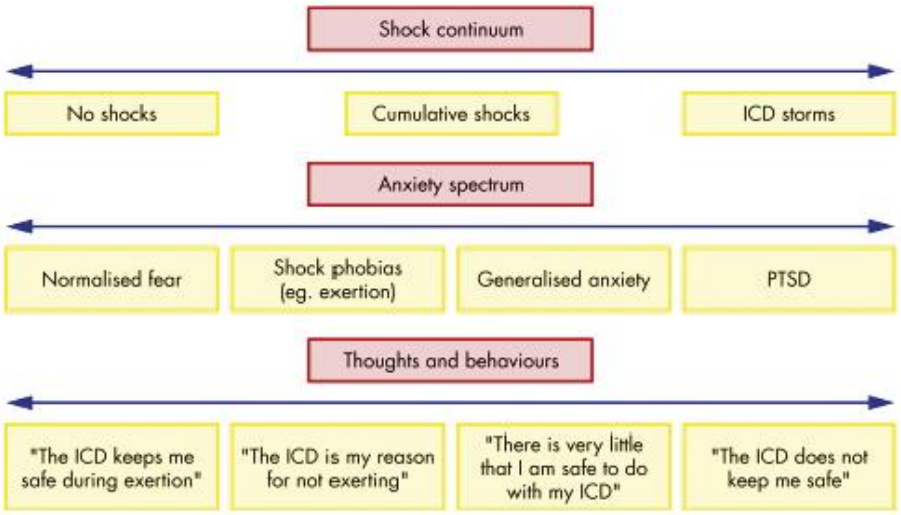

Figure 6. Continuum of ICD shock response. Reproduced from Heart, Sears SF, Conti JB, 87, 488-93, 2002, with permission from BMJ Publishing Group Ltd.

Furthermore, many patients with an ICD receive inappropriate shocks when the device delivers a high-voltage discharge for a reason other than ventricular arrhythmia. Inappropriate shocks are most commonly a result of supraventricular tachycardia including sinus tachycardia, atrial fibrillation, oversense problems (mostly due to T-waves), or technical failure [36, 37]. The incidence of inappropriate shock varies between 7-24%[12, 21, 36, 38, 39]. Recently programming strategies with a more conservative approach (i.e. higher therapy zones with longer detection intervals and more ATP therapy) have been applied, further contributing to minimizing the risk of inappropriate shocks in the future [40, 41].

Most patients tolerate ICD shocks because of the lifesaving protection provided by the device, but 23% dread shocks and 5% say they would rather be without the ICD than receive shock treatment [26].

The survival rates of ICD patients are higher than for those with a regular pacemaker. After follow-up of ten years, 66% of ICD patients were still alive compared to 36% of pacemaker patients [17]. This effect is partly due to the higher average implant age for pacemaker patients than for those who received an ICD [17]. Recently, shock therapy has been shown to increase mortality risks. The most common cause of death among patients receiving shocks was progressive heart failure [37, 42]. One potential explanation could be that shock therapy induces injury to the heart. Another could be that patients who are sicker and have poorer functional status more often experience ventricular arrhythmias and therefore receive shock therapy [43].

1.5 ICD KNOWLEDGE

There is no single definition of knowledge. In dictionaries it is defined as three components: (1) facts, information and skills acquired by a person through experience or education; (2) the sum of what is known in a field; (3) awareness or familiarity gained by experience of a fact or situation [44].

It has been shown in several studies that there is an unawareness of device benefits and indications for ICD implantation among physicians working in Cardiology and Internal Medicine and among general practitioners [45-49]. Furthermore, knowledge regarding the legal and ethical aspects surrounding therapy deactivation has also been shown to be low. In one study that surveyed physicians working in Cardiology, Internal Medicine and Geriatrics departments over 40% physicians incorrectly stated that ICD deactivation is illegal, and almost one-fifth thought deactivation was unethical. The physicians who thought deactivation was illegal were more likely to be general internists or geriatricians. However, if reassured about the legality of discontinuing ICD therapy, as many as 91% of the same respondents said they would be willing to engage in such a discussion with a dying patient [50]. Geriatricians and general internists had insufficient information about device deactivation; importantly, they were not able to identify the painful nature of shock therapy [51].

Patient knowledge about ICD indications or the benefits of their ICD treatment is also low. As many as one-third of participants in one study reported “unknown” or “no” benefits of their ICD [52].

Intervention programs – including: clinical tools, education, and standardized documentation templates in the electronic medical record – can increase rates of deactivation [53]. Early and structured education for all healthcare professionals is essential to be able to deliver a better quality of care for dying patients [54]. All physicians working with ICD patients need better knowledge about ICD functions in order to initiate and provide discussions about deactivation in terminally ill patients [55].

1.6 CARE IN END OF LIFE

The care of a patient at the end of life sometimes involves full actions with all treatment available but in the majority of patients, care at the end of life shifts to palliation [56-59]. The definition of palliative care by the World Health Organization (WHO) includes improved QOL, pain relief and management of other physical symptoms and psychosocial and spiritual issues which can affect patients who suffer a life-threatening illness [60]. Palliative care has long been a well-established option for patients affected by terminal malignancy. While cancer-related pain is well known among physicians, the incidence of pain in patients with other serious illnesses is often underappreciated. It is common for patients with advanced heart failure to have pain. One study reports such pain in up to 84% of patients with advanced heart failure [61]. An early integration of palliative care improves QOL, but can also have a possible mortality benefit [62, 63]. Heart failure patients at the end of life need relief from symptoms such as dyspnea, uremia, and depression, but they can also have a need for ICD deactivation or other mechanical circulatory support devices [64].

Prediction of death can be difficult, especially for patients with heart failure. This is due to heart failure's disease trajectory which causes the clinical course for each individual to be unpredictable. The heart failure condition is characterized by recurrent episodes of deterioration accompanied with a difficulty in anticipating the terminal phase (Figure7). Death is often sudden [54, 65-67]. Patients with advanced cancer have a more linear decline and have traditionally been the model for approaches to end-stage disease [68-70]. Studies have found that only 16% of the participating physicians said they could predict death at 6 months in heart failure patients [71]; furthermore, when these patients predict their own death, they tend to be over optimistic [72].

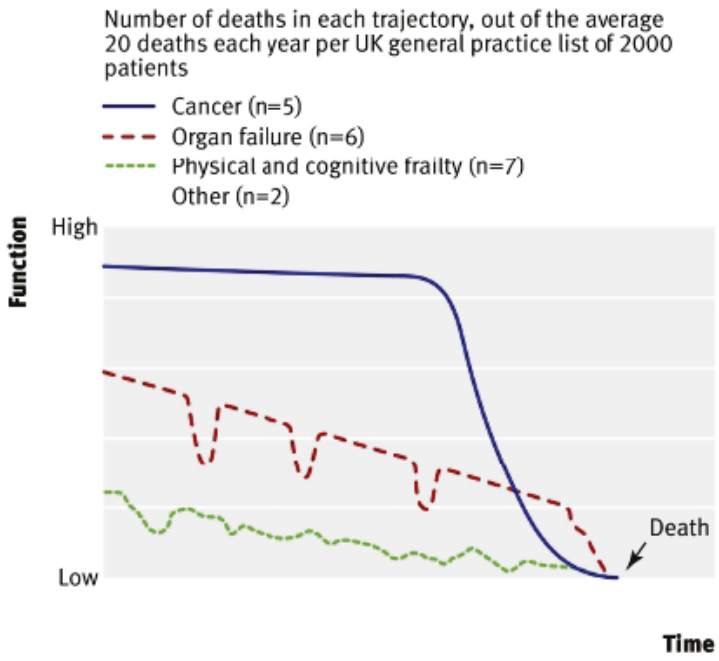

Figure 7. Trajectories of decline. Reproduced from BMJ, Murray SA and Sheikh A, 336, 958-9, 2008, with permission from BMJ Publishing Group Ltd.

1.7 LOCATION OF DEATH

Studies have shown that patients with heart failure and ICD die in hospital to a greater extent than those not treated with an ICD [73, 74]. Among those who die in a health care environment, the majority die in hospital and only a few in nursing homes or hospices [75].

1.8 DO NOT RESUCITATE

Most deaths are preceded by a long period of illness and by delivery of end-of-life care [76]. When a patient's health status deteriorates, the care shifts from lifesaving to palliative. Advance directive (AD), a legal document commonly used in USA, reflects the patient's goals, values, and wishes about their future healthcare. It goes into effect when a patient is incapacitated and unable to speak for him or herself in order to fulfill the patient's desires related to end-of-life care.[77] A Do-Not-Resuscitate (DNR) order is a request not to have cardiopulmonary resuscitation (CPR) when suffering from a cardiac arrest. A DNR order may be a part of an AD or when a patient's health status deteriorates it can be a decision issued by a physician usually together with the patient or family [78]. Even when ICD patients had an AD, very few (2%) mentioned the ICD or its deactivation. This suggests that physicians not only have to discuss this matter with patients, they also need to encourage patients to address ICD management specifically [79, 80,81], but AD are rarely used in Scandinavian countries [82] and such a document is not legally binding in Sweden [83].

Significant differences exist between Europe and North America in the management of end of life and the proportion of deaths preceded by a DNR order. These differences are characterized by wide variations between and within countries in Europe as well as between individual units [84]. In southern European countries, treatment withdrawal in the Intensive Care Unit (ICU) is less common and CPR is more often used, as compared with northern European countries [85].

1.9 DEACTIVATION

Considering deactivation of ICD therapy should take place when prolonging life is no longer the goal of care. ICD shocks can be physically painful and psychologically stressful and are therefore inconsistent with care in end of life. Deactivation of ICD therapy is both ethical and legal. No differences exist between refusing initiation of ICD therapy and requesting its withdrawal [64, 76, 81, 86]. Deactivating an ICD does not cause death; it allows the natural disease trajectory to occur [87]. Shock deactivation can be carried out either by using a special clinical magnet for temporary deactivation or permanently deactivation with a programmer [76, 81, 88, 89].

The incidence of shocks at end of life is not well studied. During the last 24 hours before death, 12% of patients in one study received shock treatment [90]. In another study, family members reported that 6% of the patients received a shock within minutes before death [91].

Patients have a poor understanding of ICD function. Almost two-thirds of the patients think that the device needs to be explanted in order to be deactivated [92]. Most cardiologists have almost contradictory beliefs about patient understanding of ICD functioning. The vast majority (93%) of cardiologists believe that patients understand how the ICD functions and are aware of the possibility to deactivate the device [93]. Furthermore, patients' own opinions about deactivation differ [94]; some patients favors deactivation [95], and some do not [92, 96]. Deterioration in health status does not seem to effect patients' attitudes towards deactivation. Even when suffering from terminal cancer, patients did not want deactivation as they were still hopeful of a cure and therefore prolonged life [97]. Patients' misconception of the ICD's true lifesaving capacity often manifests itself in their overestimating the ICD's capability of preventing death. Patients sometimes even think about deactivation as an act of suicide [82, 92, 96, 98-100]. Even when patients seem to understand the role of an ICD, the decisions are made more intuitively than rationally. When asked about their willingness to deactivate their ICD, patients answered 'no'. They were unwilling to deactivate because they believe ICD prevents SCD, which is understood as a preventative measure against any death. When the same patients are asked if they prefer a slow death, some answer 'no' to this as well [101].

Discussion regarding ICD deactivation should be proactive and held continuously, before device implantation and at any major change in patient health status [81, 102]. Despite this, physicians rarely discuss therapy deactivation with their ICD patients. This is also reflected in several studies in which a large majority of physicians think that deactivation of ICD in terminally ill patients is reasonable but rarely discuss it routinely [103-105]. Physicians have limited experience; in Cardiology departments 60% of physicians had two or fewer conversations about deactivation with patients and families. For physicians in Internal Medicine and Geriatrics, the great majority (95%) reported to have had such conversations [71]. Electrophysiologists are the ones who most often initiated discussions, but only 20% actually do engage in these discussions [51]. Despite the lack of reported conversations, physicians do not feel that discussion about ICD deactivation is distressing for patients and their families. On the other hand physicians do believe that shock treatment is distressing [51]. Even with this belief, physicians are less comfortable with ICD deactivation than discontinuing other lifesaving treatments [106]. Even though some physicians admit being uncomfortable with deactivations they have performed [107] prior experience with deactivation is the strongest predictor of physician willingness to initiate future discussions regarding deactivation [51, 108].

Some patients find it unlikely that discussions will lead to increased anxiety [92, 95], but others feel they never want to engage in such discussions [82, 98]. Experience of shock treatment is associated with a more positive attitude towards discussion about it [92].

1.10 CAUSE OF DEATH

Most common cause of death for patients with cardiac disease is acute myocardial infarction, a condition that often involves life-threatening arrhythmic events [3]. Many

patients who develop heart failure do so as a consequence of a myocardial infarction [109]. The survival rate in heart failure is comparable with many cancer diagnoses, but the trajectory at end of life differs between the two diagnoses [70].

The most common definition of sudden death is if death occurs within one hour of the onset of new symptoms [110]. Epstein et al, have developed a scheme for the classification of death which is used in trials of antiarrhythmic treatments, using the following categories: primary organ cause, temporal course, documentation, operative relation and system relation [111].

Cardiac death is the major cause of death among ICD patients [7, 74, 112, 113]. Mode of death was assessed for a total of 320 deaths of ICD patients participating in trials of Medtronic. The cause of death was: sudden in 28% of the patients, non-sudden cardiac death in 49% and 22% were regarded as non-cardiac deaths [113]. The arrhythmic incidence at death in the ICD population is not well studied, and the few studies that have been done have shown that VT or VF occurred in 28-66% of patients before death [113-115].

2 AIM

OVERALL AIM:

The overall aim of this thesis was to study patients with implantable defibrillator in end of life as well as physicians' knowledge about ICD therapy and compliance to guidelines concerning ICD management.

SPECIFIC AIM:

I. To analyze explanted ICD from deceased patients to assess the incidence of ventricular tachyarrhythmias, the occurrence of shocks, and possible device malfunction before death.

II. To investigate end of life in ICD patients with a DNR order, with respect to location of death; duration between DNR order and therapy deactivation; or DNR and time of death.

III. To assess the levels of knowledge concerning ICD therapy among physicians active in Cardiology, Internal Medicine and Geriatrics.

IV. To investigate if deactivation of shock therapy in ICD patients at end of life has increased since publication of new guidelines on ICD management.

3 MATERIAL AND METHODS

3.1 STUDY I

The study prospectively enrolled 130 ICD devices during the inclusion period from 26 pathology departments. Demographic data were obtained from patients' medical notes, The Swedish ICD and Pacemaker Registry and The National Board of Health and Welfare. Death certificates which state location, time and cause of death, were obtained from the Swedish Tax Agency. Autopsies, if performed, were also collected.

The time of death was established from medical notes for patients who died in hospital. Time of death for patients who died at home was assessed from death certificates together with notes from palliative care teams when available. If death was witnessed the time was considered to be correct.

All available intracardiac electrograms (EGM) from the last 24 hours were retrieved from the ICD. After analysis from the manufacturer, five devices were excluded due to inaccessible data. Three investigators – two of whom were blinded to patients' medical history individually reviewed and analyzed all arrhythmias. If there was a disagreement of origin of the arrhythmia, a fourth blinded investigator proceeded and consensus was made if three out of four investigators agreed upon the origin. The incidence of ventricular tachyarrhythmia and shock treatment within the last 24 hours of life was recorded. If the patient had VT or VF present within 1 hour of death and if the arrhythmia was classified as the primary cause, it was classified as an arrhythmic death. Definition of an arrhythmic storm was the occurrence of three or more episodes of VT/VF within a 24-hour period [20].

To classify the cause of death, two investigators used a modified classification scheme made for ICD patients in arrhythmia trials [111]. The classification of device function depended on success in diagnosis, treatment given, and also if there was any evidence of lead malfunction.

3.2 STUDY II

This study is a descriptive analysis of 65 deceased ICD patients all with a DNR order present before death. The study population was drawn from the 125 patients in study I, and included all those with a written DNR order or who were in palliative.

Patients' location of death were identified – i.e. home, nursing home, hospice or in hospital. If a patient died in hospital, the type of hospital – university or non-university – as well as the specialty of the ward in which the patient was admitted when death occurred was also identified. A hospital was defined as a university hospital if the hospital had an affiliation with a university and provision of clinical education for medical students in addition to delivering patient care. Ward specialty was categorized as Cardiology, Medicine (including Infection, Oncology and Intensive Care Unit), Surgery and Geriatrics.

The time of death for patients dying in hospital was established from medical notes and from death certificates. For patients dying at home, the time of death was assessed from the death certificate and, if available, notes from the palliative care team, if death was witnessed, the time of death was considered as correct. The time from the decision to issue a DNR order and therapy deactivation as well as time to death were analyzed.

Date of deactivation was collected from medical notes together with information retrieved from the post-mortem interrogation of the ICD devices. Shock treatment within 24 hours of death was classified as shock at end of life. In addition to the occurrence of any shocks, we assessed the number of shocks received during the last 24 hours of life. Classification of death was made using the same model as in study I.

3.3 STUDY III

This is a cross-sectional comparative study. A questionnaire was constructed by the research group and distributed to physicians in Cardiology, Internal Medicine and Geriatrics departments, the three most common ward specialties in study I and study II. In the early phase of item construction three focus groups discussions were held with physicians from all three specialties. The focus groups were semi-structured and focused on necessary ICD knowledge for a physician working in each specialty. The first item pool was modified after tested on ten clinical ICD experts. The instrument underwent a pilot test with physicians in all three specialties within Danderyds Hospital. Most respondents felt that the questionnaire was clearly worded and well designed. The majority agreed that the instrument measured the level of knowledge regarding ICD treatment. After minor revisions based on the pilot results, the instrument consisted of 51 items and was considered to have a good face and content validity. Twenty of those 51 items were specific knowledge questions, sixteen were related to international guidelines awareness and 14 were of a descriptive nature.

Level of sufficient knowledge was defined in a weighting process by the research group and by 10 clinical ICD experts. It resulted in nine questions viewed as necessary knowledge for physicians who care for patients with ICD. To achieve sufficient knowledge on the questionnaire the respondents had to answer seven out of the nine necessary knowledge questions correctly.

A stratified nationwide cluster sampling of hospitals was performed in which hospital size and geographic spread were taken in to account. Written consent was obtained from each clinical director. In order to maximize the response rate the investigators arranged with the directors in each clinic to attend a regular closed meeting with the physicians in which questionnaires were handed out and collected manually. The participants had in most cases no prior knowledge about the distribution of the survey until the meeting started.

3.4 STUDY IV

This is a descriptive study drawn from two cohorts of ICD patients, all of whom died in Swedish hospitals before and after the implementation of international guidelines on management of ICD patients nearing end of life, which were published in 2010 [76, 81].

Study agreements were obtained from all participating hospitals, and the medical records from the final 24 hours of life were obtained for all patients. Data from the Swedish ICD and Pacemaker Registry and death certificates, which state time and location of death, were obtained from the Swedish Tax Agency.

Type of hospital and ward specialty in which the patients died was identified. Definition for university hospital was the same used in study II. Type of ward specialty was categorized as Cardiology (including Cardiac Intensive Care Unit and Thoracic Intensive Care Unit) or Non-Cardiology (including Medicine, Intensive Care Unit, Acute and Emergency Department and Geriatrics). Patients who died in nursing home, hospice or at home were excluded. Patients who had their ICD explanted or deactivated more than 1 month prior to death were also excluded.

The population for group 1 was drawn from the 125 patients in study I who died between 2003-2010 before the guidelines where published. It consists of the 89 patients who died in hospital. During 2014, there were a total of 464 ICD patients who died in Sweden. Of those, 253 died in hospitals and 246 of these patients were included in group 2. One out of 63 hospitals with seven patients decided not to participate in the study.

The same classification of death used in study I was used in group 2 and performed by the same two investigators, with an additional investigator in cases of disagreement.

4 STATISTICAL ANALYSIS

Continuous variables are presented as mean and standard deviations (SD) or median with Interquartile Range (IQR) as appropriate and for categorical variables percentages or as confidence interval of proportions.

Differences between means were tested using independent t-test. For between group comparisons, we employed Mann-Whitney test for continuous variables, Pearson chi-square or Fisher exact tests for smaller sizes were applied to categorical variables. One-way analysis of variance (ANOVA) was used to compare means between groups.

A statistical power analysis for sample size estimation was performed for each study. Statistical significance was set at two-sided p less than or equal to 0.05. All statistical analysis was performed using SPSS software Version 20-22.

4.1 ETHICAL CONSIDERATIONS

Study I, II and IV were approved by the Regional Ethics Committee (2008/1527-31/4, 2014/1787-32/4).

An ethical approval for study III was sought but the Ethics Committee did not consider an ethical application necessary, as the questionnaire involved healthcare professionals only and not patients.

5 RESULTS

5.1 STUDY I

This is a descriptive study of 125 ICD patients who died during 2003-2010 in Sweden. Deactivation of therapy 24 hours before death was done in 25 cases with no further possibility to detect an arrhythmia in these patients. Results regarding VT/VF at 24 hours are therefore based on a study population of 100 patients (Figure 8).

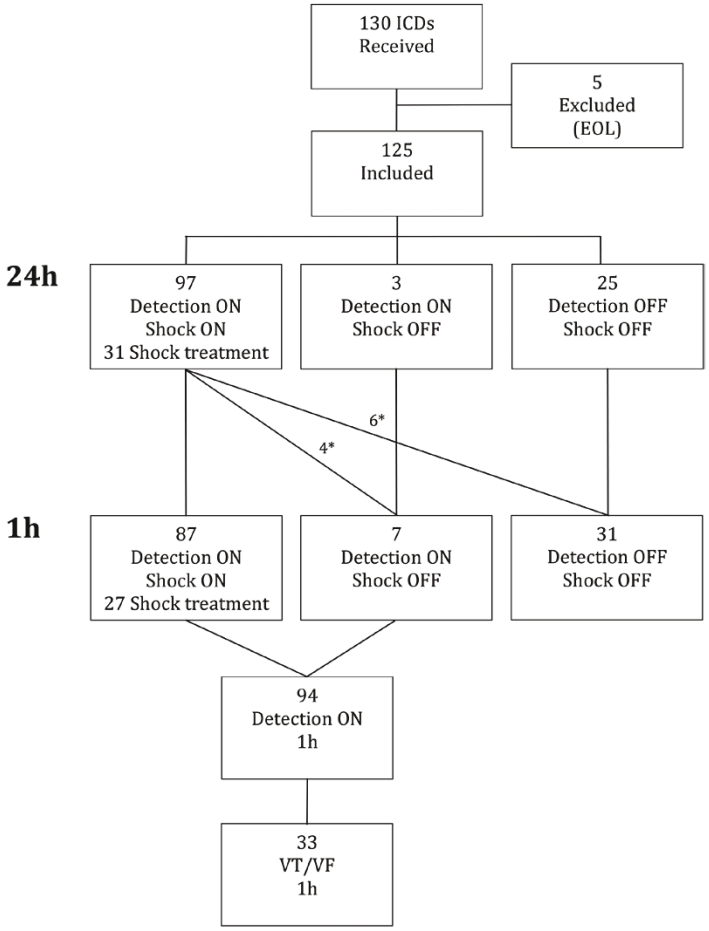

Figure 8. Inclusion, exclusion, arrhythmia detection and shock therapy given at 24 hours and 1 hour before death. EOL indicates end of life; ICD, implantable cardioverter defibrillator; and VT/VF, ventricular tachycardia/ventricular fibrillation. *Change in programming during the last 24 hours. Circulation. 2014 Jan 28;129(4):422-9. Wolters Kluwer Health Lippincott Williams & Wilkins© No modifications will be permitted.

The majority (82%) of patients had received an ICD due to secondary prevention. Device implantations were performed between 1998-2010. Just over one-third (35%) of those patients had CRT-D devices. Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics. Circulation. 2014 Jan 28;129(4):422-9. Wolters Kluwer Health Lippincott Williams & Wilkins© No modifications will be permitted

	All n=125	Detection ON 24h n=100
Male	111(89)	87(87)
Age at death, y, mean± SD	74±9	74±9
Morbidity*		
Hypertension	30(24)	22(22)
Ischemic heart disease	91(73)	76(76)
Acute myocardial infarction	85(68)	70(70)
Heart failure	116(93)	91(91)
Diabetes mellitus	43(34)	38(38)
Chronic pulmonary disease	27(22)	22(22)
Chronic kidney disease	42(34)	33(33)
Tumor	22(18)	13(13)
Ejection Fraction		
EF ≥55%	6(5)	4(4)
EF 45-54%	10(8)	10(10)
EF 30-44%	38(30)	32(32)
EF <30%	68(54)	52(52)
Not known	3(2)	2(2)
Medications†		
ACE inhibitor	94(75)	77(77)
Diuretics	118(94)	94(94)
β-Blocker	111(88)	90(90)
Calcium antagonist	7(5)	6(6)
Amiodarone	47(37)	39(39)
Aspirin	61(48)	48(48)
Clopidogrel	4(3)	3(3)
Warfarin	60(48)	51(51)

Values are listed as values n (%)

* Based on international classification of diseases in the medical notes. Not cause of death.

A DNR order accompanied 52% of the patients. The vast majority of the patients were treated in a care facility, seventy-one percent of which in hospital, and only 19% of the patients died at home.

Ventricular arrhythmia (VT/VF), was found in 33 (35% (95% CI 25%; 46%)) patients during the last hour, and shock was delivered in 27 (31%) patients. An arrhythmic storm was evident in 24 (24%) patients and 79% of them received shock treatment.

Patients receiving shock often had many shocks; 45% had 1-2 shocks and 55% had 3 shocks or more. There were 10 (32%) patients who each experienced more than 10 shocks.

ICD therapy was still active in 42 (65%) of the 65 patients with a DNR order and 10 (24%) of these patients received shock therapy during their last 24 hours. The number of shocks is presented in Table 2.

Table 2. Distribution of shocks in patients with DNR order*. Circulation. 2014 Jan 28;129(4):422-9. Wolters Kluwer Health Lippincott Williams & Wilkins© No modifications will be permitted.

	Adequate shock	Number of shocks
Patient 1	yes	2
Patient 2	yes	1
Patient 3	yes	6
Patient 4	yes	1
Patient 5	no†	2
Patient 6	yes	6
Patient 7	yes	1
Patient 8	no‡	42
Patient 9	yes	18
Patient 10	yes	1

DNR indicates Do-Not-Resuscitate
* All DNR orders written before shock treatment
† Inadequate shock treatment due to oversense
‡ Inadequate shock treatment due to Atrial fibrillation

Inappropriate therapy was given to 4 (13%) patients. For the majority of patients, there was no evidence found suggesting that they, their family or their health care professionals had recognized that shock was delivered. However in 39% of patient cases, a notification was found which stated that the health care provider had recognized the shock treatment or that the patient had showed signs of pain or stress during the last hours, which is possibly indicative of shock therapy.

Cardiac death (59%) was found to be the most common cause and heart failure (37%) the most specific cause of death. Arrhythmic death was the primary cause in 13% of patients. For 23% of patients the death was classified as sudden.

5.2 STUDY II

All 65 patients had a DNR order and died between 2003-2010. Secondary prevention was indication for the initial ICD implantation in 78% of patients.

Hospital was the location of death for 86% of patients. Many of those were university hospitals. All but two patients had access to healthcare assistance during the last days of life. For one patient the location of death was unknown (Figure 9).

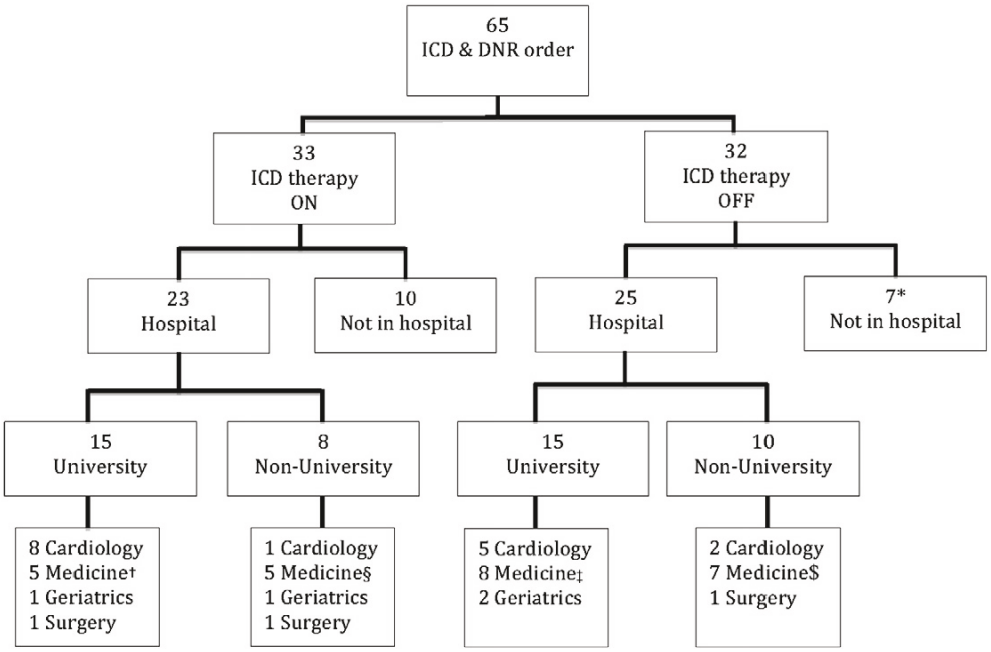

Figure 9. Location of death and active or deactivated therapy in 65 patients with a DNR order. *One patient's location of death is missing. †Medicine ward including Oncology (1), §Medicine ward including Infection (1), Intensive Care Unit (2). ‡Medicine ward including Intensive Care Unit (1). $Medicine ward including Oncology (1). ICD indicating Implantable Cardioverter Defibrillator. Reprinted from Int J Cardiol. 2015 Mar 1;182:440-182, Kinch Westerdahl et al, Defibrillator patients should not be denied a peaceful death, Copyright 2015, with permission from Elsevier.

During the last 24 hours, as many as 24% (95% CI,11%-37%) of patients received shock treatment despite the decision to refrain from resuscitation (Table 3**)**.

Table 3. ICD therapy programmed ON or OFF in different locations (n=65). Reprinted from Int J Cardiol. 2015 Mar 1;182:440- 182, Kinch Westerdahl et al, Defibrillator patients should not be denied a peaceful death, Copyright 2015, with permission from Elsevier..

	All	**Medicine**	**Cardiology**	**Geriatrics**	**Surgical**	**Hospice (4) Nursing Home (4)**	**Home (8) Not known (1)**
	n=65	n=25	n= 16	n= 4	n=3	n=8	n=9
ICD ON 24h	42(65)	15(60)	12(75)	2(50)	3(100)	5(63)	5(56)
ICD ON 1h	33(51)	10(40)	9(56)	2(50)	2(67)	5(63)	5(56)
ICD OFF 1h	28(43)	13(52)	5(32)	2(50)	1(33)	3(38)	4(44)
Magnet	4(6)	2(8)	2(13)	0	0	0	0
Shock *	10(24)	5(33)	2(13)	1(25)	1(33)	1(13)	0†

Values are listed as values n (%)
*Shock during the last 24h for patients with ICD ON 24h
†1 Aborted shock

Deactivation was performed in 49% of the 65 patients, most of them within 24 hours of a DNR order, but for 19% a week or more passed between decision of DNR and deactivation.

The durations between DNR order and death for patients receiving shock therapy are presented in Table 4.

Table 4. Hospital, ward specialty and number of shocks (n=10). Reprinted from Int J Cardiol. 2015 Mar 1;182:440- 182, Kinch Westerdahl et al, Defibrillator patients should not be denied a peaceful death, Copyright 2015, with permission from Elsevier.

	University Hospital	Ward specialty	Time from DNR to death	Number of shocks
Patient 1	Yes	Cardiology	2 days	2
Patient 2	Yes	Geriatrics	90 days	1
Patient 3	Yes	Cardiology	<24h	6
Patient 4	No	Nursing home	38 days	1
Patient 5	Yes	Medicine (Oncology)	4 days	2
Patient 6	Yes	Medicine	4 days	6
Patient 7	No	Medicine (Oncology)	15 days	1
Patient 8	Yes	Medicine (Neurology)	1 day	42
Patient 9	No	Medicine (ICU)	1 day	18
Patient 10	No	Surgery	<24h	1

ICU indicating Intensive Care Unit
DNR indicating Do-Not-Resuscitate order

Cardiac deaths were the cause in about half (52%) of patients in which heart failure was the most common (42%) specific cause. For the non-cardiac cause, malignancy (23%) was most common.

5.3 STUDY III

A total of 432 surveys were distributed and 430 collected. Only two physicians did not submit the survey after completion, resulting in a response rate of 99.5%. Distribution was done in 14 (78%) of 18 of the sampled hospitals, five (36%) of which were university hospitals. Out of the sampled hospitals, four either did not respond or declined participation to the enquiry of participation.

A total of 83% of physicians said they had earlier experience with ICD patients, but 68% estimated their level of knowledge about ICD treatment to be low. Baseline characteristics are presented in Table 5.

Table 5. Baseline characteristics.

	All n=430	Cardiology n=139	Medicine n=184	Geriatrics n=107
Men(n=428)	226(53)	99(71)	93(51)	34(32)
Age(n=417)	42.9±11.0	45.0±10.2	41.6±10.5	42.3±12.6
Years since graduation(n=401)	14.8±11.0	17.5±10.3	13.1±10.5	14.4±12.3
University hospital(n=430)	165(38)	98(71)	51(28)	16(15)
Level of education(n=428)				
Medical Intern	85(20)	16(12)	35(19)	34(32)
Fellow	100(23)	27(19)	55(30)	18(17)
Attending physicians	243(57)	96(69)	92(50)	55(51)
Years as attending physician	12.9 ±8.8	13.6±8.1	12.1±10.0	12.9±8.8
Specialist ≥10 yrs.	142(58)	64(67)	46(54)	32(58)
Self-estimated level of knowledge(n=422)				
Low/very low	288(68)	51(37)	142(79)	95(90)
Good/very good	134(32)	86(63)	37(21)	11(10)
Experience treating patients with ICD(n=423)				
Never	74(17)	5(4)	40(22)	29(27)
1-10 times/yr.	240(57)	52(37)	123(67)	65(61)
11-≥21 times/yr.	109(26)	79(57)	20(11)	10(9)
Experience treating patients at end of life(n=425)				
Never	37(9)	8(6)	21(11)	8(8)
1-10 times/yr.	156(36)	61(44)	63(34)	32(30)
11-≥21 times/yr.	232(54)	68(49)	99(54)	65(61)
Number of discussions about ICD deactivation(n=425)				
Never	225(52)	36(26)	121(66)	68(64)
Seldom	168(39)	72(52)	61(33)	35(33)
Often	32 (7)	30(22)	1(1)	1(1)
Deactivation is ethically permissible(n=420)				
Agree completely	349(81)	113(84)	153(80)	83(80)
Deactivation is legally permissible(n=420)				
Agree completely	385(90)	123(92)	167(87)	95(91)
Patients have the right to refuse treatment/request withdrawal(n=424)				
Agree completely	312(73)	100(75)	136(71)	76(73)

Data given as mean ± SD or n (%)
Total number of responses for each question listed as values n
ICD indicating Implantable Cardioverter Defibrillator

A significant difference in level of knowledge was found between physicians in different specialties. A total of 41% of all physicians reached sufficient level of knowledge according to the predefined criteria of necessary knowledge for the ability to manage patients with ICD. The physicians working in Cardiology departments scored higher than other physicians and had an average score of 6.79 ±1.75 out of nine possible correct answers. Compared to other physicians they earned 1.82 (CI 1.43-2.20) points higher. Physicians in Internal Medicine scored significantly ($p<0.001$) better than physicians in Geriatrics. Furthermore, physicians in university hospitals had significantly ($p<0.001$) higher scores with a mean of 6.23 ± 1.99 than

non-university hospitals. Attending physicians had higher scores ($p<0.001$) compared to fellows in all fields (Table 6).

Table 6. Mean score between level of education and specialty.

Specialty	Mean score	SD	Sign (2-tailed)	Mean difference	95% Confidence Interval	
Cardiology (n=139)	6.79	±1.75	<0.001	+1.82	+1.43	+2.20
Fellow (n=27)	5.70	±1.88	<0.001	-1.81	-2.30	-1.30
Attending physician (n=96)	7.51	±0.91	<0.001	+1.81	+1.30	+2.31
Internal Medicine (n=184)	5.24	±1.94	0.004	-0.57	-0.96	-0.18
Fellow (n=55)	5.38	±2.04	N.S	-0.19	-0.82	+0.44
Attending physician (n=92)	5.58	±1.76	N.S	+0.19	-0.44	+0.82
Geriatrics (n=107)	4.53	±1.89	<0.001	-1.38	-1.81	-0.94
Fellow (n=18)	4.56	±2.28	N.S	-0.34	-1.44	+0.75
Attending physician (n=55)	4.89	±1.92	N.S	+0.34	-0.75	+1.43

Total number of responses for each group listed as values n

Only 76% of physicians indicated shock treatment as being painful if experienced by a conscious patient. This knowledge was indicated even less among physicians in specialties other than Cardiology: 69% in Internal Medicine and 67% in Geriatrics. An insecurity regarding SCA was shown in that 40% of all doctors said they did not know how to handle an ICD patient with SCA and 29% agreed with the following statement: "You can not externally defibrillate a pulseless ICD patient." See Table 7 for the results on all nine weighted knowledge questions.

The two internationally accepted abbreviations used for implantable defibrillators are ICD and CRT-D. Only 24% of respondents identified both abbreviations, and 10% of them failed to identify any. Just over half (51%) of physicians in Cardiology, 14% of physicians in Internal Medicine and 6% in Geriatrics could identify both. When asked about their awareness of international ICD guidelines, many physicians – 77% of all and 38% of them in Cardiology – estimated it to be poor or very poor. Patients with ICD treatment have some legal restrictions on the conditions under which they are allowed to operate a motor vehicle. Almost half (49%) of the respondents did not know that it is prohibited for an ICD patient to drive commercials vehicles.

In regards to the following statement: "Patients always have the right to refuse treatment, seventy-three percent agreed ("I agree completely") while only 3% disagreed ("I completely disagree").

Table 7. Sufficient knowledge between medical specialties (correct answer in seven out of nine necessary questions).

Question	All n=430	Cardiology n=139	Medicine n=184	Geriatrics n=107
1. An implant defibrillator primarily helps patients to counteract sudden death (True) (n=425)	382(90)	131(94)	165(90)	86(80)
2. The pacing function will be temporarily deactivated by placing a magnet over an ICD (False) (n=426)	150(35)	84(60)	45(25)	21(19)
3. Shocks can be temporarily deactivated by placing a magnet over an ICD (True) (n=426)	292(69)	121(87)	109(59)	62(58)
4. Shock treatment from an ICD is painful for a conscious patient (True) (n=426)	324(76)	125(90)	127(69)	72(67)
5. It is dangerous for another person to be in physical contact with a patient receiving ICD shocks (False) (n=421)	342(81)	127(91)	145(79)	70(65)
6. Due to safety precautions it is not possible to deactivate the ICD shock treatment (False) (n= 422)	304(72)	118(85)	122(66)	64(60)
7. If ICD shock therapy is deactivated the pacemaker function in the device will also be deactivated (False) (n=423)	287(68)	121(87)	113(61)	53(50)
8. If ICD shock therapy is deactivated, shocks can not be activated again. (False) (n=423)	318(75)	124(89)	138(75)	56(52)
9. I may externally defibrillate a pulseless ICD patient. (True) (n=416)	293(70)	113(81)	126(69)	54(51)
Sufficient knowledge (n=428)	**175(41)**	**99(71)**	**56(30)**	**20(19)**

Values are listed as values n (%)

Correct answer for each question listed within brackets

ICD indicates Implantable Cardioverter Defibrillator

5.4 STUDY IV

Inclusion, exclusion criteria and distribution of DNR order and deactivation is shown in Figure 10.

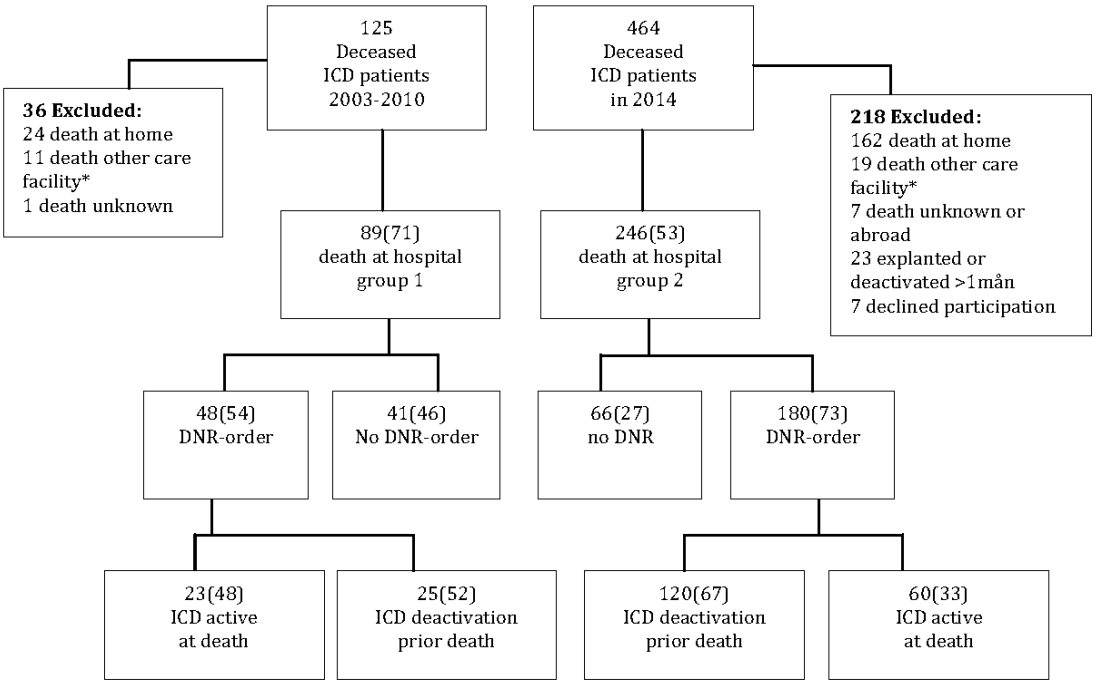

Figure 10. Inclusion, exclusion.Values are listed as values n (%) DNR indicating Do-Not-Resuscitate; ICD indicating Implantable Cardioverter Defibrillator; * Other Care facility indicating hospice or nursing home.

No significant difference was found between groups regarding age or gender distribution. Co-morbidities between the groups were similar, with the only significant difference found for hypertension ($p=0.013$), which was more frequent in group 2. The primary prophylactic indication for ICD treatment significantly ($p<0.001$) differed between groups. Baseline characteristics are presented in Table 8.

Table 8. Baseline characteristics.

	Group 1 n=89	**Group 2** n=246	**p-value**
Male	77(87)	203(83)	N.S
Age at death (yrs.)	73.8 ±8.8	72.8 ±8.7	N.S
Duration ICD treatment (yrs)	3.4 (IQR 1.6-6.1)	4.1 (IQR 1.8-6.3)	N.S
Morbidity†			
Hypertension	21(24)	94(38)	0.013
Ischemic heart disease	67(75)	185(75)	N.S
Acute Myocardial Infarction	60(67)	142(58)	N.S
Heart Failure	83(93)	223(91)	N.S
Diabetes mellitus	29(33)	94(38)	N.S
Chronic pulmonary disease	22(25)	47(19)	N.S
Chronic kidney disease	36(40)	114(46)	N.S
Malignancy	16(18)	53(22)	N.S
Stroke	8(9)	40(16)	N.S
Ejection Fraction			N.S
EF ≥55%	5(6)	13(5)	
EF 45-54%	5(6)	11(5)	
EF 30-44%	26(29)	70(29)	
EF <30%	51(57)	146(59)	
Unknown	2(2)	6(2)	
ICD indication			
Primary prevention	15(17)	111(45)	<0.001
CRT-D	30(37)	107(44)	N.S

Values are listed as values n (%)

† Based on international classification of diseases in the medical notes. Not cause of death.

Patients in group 1 died in 26 different hospitals, 10 of which (38%) were university hospitals. For group 2, university hospitals represented 11 (17%) out of 63 total hospitals. There was a similar distribution in both cohorts of patients' treatment location: for groups 1 and 2 respectively, 37% versus 31% of patients were treated in Cardiology and 63% versus 69% were treated in Non-Cardiology wards (Table 9).

Table 9. ICD therapy deactivation and DNR in different locations.

	Group 1 (n=89)	**Group 2** (n=246)	**p-value**
DNR	48(54)	180(73)	0.009
Deactivation	30(34)	126(51)	0.005
DNR & ICD Deactivation	25(52)	120(67)	N.S (0.062)
Cardiology*	**33(37)**	**76(31)**	**N.S**
DNR	17(52)	54(71)	N.S
Deactivation	12(36)	48(63)	0.010
DNR & Deactivation	8(47)	42(78) †	0.016
Non-Cardiology	**56(63)**	**170(69)**	**N.S**
DNR	31(55)	126(74)	0.044
Deactivation	18(32)	78(46)	N.S
DNR & Deactivation	17(58)	78(62)†	N.S

Values are listed as values n (%)

* Including Cardiac Intensive Care Unit and Thoracic Intensive Care Unit

† Differences in deactivation within group 2 between Cardiology vs. Non-Cardiology was significant (p=0.038). DNR indicating Do-Not-Resuscitate order; ICD indicating Implantable Cardioverter Defibrillator.

Cardiac death was the most common cause and heart failure was the most common specific cause of death with no significant difference between groups. More system related deaths were found in group 1 than in group 2. Technical malfunction in group 2 is based on medical notes and not actual device interrogation as it is in group 1.

Over half (54%) of the patients in group 1 had a DNR order, and 52% of them had shock therapy deactivated. In group 2 there were 73% of patients who had a DNR order, and shock therapy was deactivated in 67% of patients. Although there were a general increase in shock deactivation between groups for patients with DNR the difference was not significant (p=0.062), but increased significantly (p=0.016) between group 1 and group 2 among patients treated in Cardiology wards (Table 9). A significant difference (p=0.038) in deactivation rate for DNR patients was found within group 2 between patients treated in Cardiology vs. Non-Cardiology wards. No such difference was found within group 1. Deactivation of shock therapy was performed after two days or more in about 40% of patients in both groups.

6 DISCUSSION

We have shown that patients with ICD often have ventricular tachyarrhythmia and suffer from shocks close to death. Patients were at end of life and many had a DNR order; despite this ICD shock therapy remained active in the majority of the patients. In hospital death was most common and the majority of patients were treated in Non-Cardiology wards. There was a lack of basic knowledge of ICD therapy among physicians. Knowledge gaps were most considerable among physicians in Internal Medicine and Geriatrics departments. Newly published international guidelines on the management of ICD patients in end of life have had some impact but mainly among physicians in Cardiology.

Ventricular tachyarrhythmia

In study I we have shown that ventricular tachyarrhythmia is not uncommon in dying ICD patients. One-third of the patients had VT or VF and almost one-fourth had arrhythmic storm during the last day of life. Many terminally ill patients develop conditions pre-disposing them to arrhythmia [76]. It is well know that heart failure patients' deaths often come suddenly [54, 65-67]. New York Heart Association class (NYHA) III is an independent predictor of shock treatment [116]. The patients' NYHA class is not known in our studies; however, while over 50% of all patients had EF<30%, one can assume NYHA class to be III or less. The temporal cause of death was similar in both study I and study IV, comparable to the results in MADIT-II, in which death was sudden for over one-fourth of patients [74]. Cardiac death and heart failure, was the most common cause of death in study I and study IV. This result shares a similar distribution to previous ICD studies [113, 117]. Arrhythmic death was the cause of death in only 13% of patients.

Shock

Almost one-third of the patients in study I received shock therapy during the last hour of life and those who received shock often received multiple shocks. Despite a DNR order in the majority of patients, shock therapy was active in half of the patients 24 hours before death, exposing patients to a risk of unnecessary shock treatment. In study II, in which all patients had a DNR order, one-fourth of patients received shock therapy during the last day of life.

Most patients find ICD shocks painful and frightening, leading to lower QOL, with anxiety and distress [22, 23, 26-28, 32, 118, 119]. It is not known to what extent shocks cause pain in dying ICD patients, but healthcare providers have a responsibility to minimize pain in palliative patients [60]. It is imperative that patients understand that therapy deactivation is an option. The majority of physicians in study III do acknowledge that shocks are painful for a conscious patient, but one-third of physicians in Medicine and Geriatrics did not. The unawareness of

this important complication could possibly prolong the time before patients receive adequate care and support in case of shock.

DNR order and ICD patients at end of life

When a patient life is ending and illnesses can't be cured, the focus of care shifts from curability to palliation. Palliative care includes relieving the patient from pain and other distressing symptoms [60]. The majority of patients in study I and study IV had a DNR order, confirming earlier studies which show that dying patients commonly have DNR order [58, 59]. The purpose of a DNR order is to support patient autonomy and to prevent non-beneficial interventions. Old age, perception of a poor prognosis and impaired functional status have shown to correlate with patients' wish to not want resuscitation [57, 120]. Physicians' willingness to make decisions regarding DNR is influenced by their experience as well as a history of prior end of life discussions [51, 108, 121].

Patients' involvement in the DNR process is not known in our studies. Prior studies have shown an inconsistency in patients' willingness to engage in end of life discussions; there are those who want to be involved in such discussions and those who do not [92, 95, 122, 123]. Despite this, physicians often make decisions regarding DNR and deactivation without involvement of patients or family, an approach more common in Sweden than in other European countries [76, 104, 124, 125]. Not involving the patient is probably a decision made based on the assumption that resuscitation is futile for the patient concerned. Interestingly, there is an inconsistency about patients' preferences for therapy outcome. Some studies suggest that treatment resulting in improved symptoms is of greater importance than treatment resulting in longer survival while others show that patients preferred survival longevity over QOL [96, 126]. Nevertheless, patients' involvement in end of life conversations leads to less intensive medical interventions, fewer admissions to ICU and fewer patients undergoing CPR [127]. ICD due to primary prevention, advanced age, earlier experience of shocks or an awareness of being at the end of life are characteristics shown to more easily enable discussions with patients [80, 82, 95, 99, 122]

Deactivation

Almost half of the patients with a DNR order in study I and one-third of the patients in study IV (group 2) died with active ICD therapy. Although a DNR order is not equal to ICD deactivation, it is an essential factor in initiating a discussion [76].

The exact number of patients who died with active therapy and who had a prior conversation about deactivation in our studies is not known. Communication regarding therapy deactivation is complicated, but should be done early, systematically and continuously over the course of a patient's illness. Physicians do acknowledge the importance of discussing

deactivation with dying ICD patients, even though many are reluctant to engage in these discussions [87, 103].

Both patients and physicians find ICD deactivation morally equivalent to a DNR order in that deactivation allows the patient to die of the natural progression of their underlying disease [76, 89]. Physicians believe that patients know that deactivation is a possible option, but most patients are not aware of this [92, 93, 100]. Physicians and patients are also unaware about the function of the ICD if deactivated, which contributes to this issue's complexity [50, 51, 82, 95, 97, 98].

Patients always have the right to refuse treatment and withdrawal of ICD therapy at any time [36, 76, 81, 128]. The majority of physicians in study III agreed to this as well as the ethicality and legality of deactivation in a terminally ill patient, which is inline with international guidelines [66, 76, 81, 89].

Study IV showed that the number of deactivations has increased for DNR patients admitted to hospital since the start of study I, though the increase was not significant. For DNR patients treated within Cardiology however the increase over the years was significant. Furthermore, DNR patients who were in group 2, treated in Cardiology wards and who died in 2014 all had higher rates of deactivations compared with those who were treated in Non-Cardiology wards. These results imply that international guidelines possibly helped in the management of patients in Cardiology but did not help for patients managed in other specialties. During the last 5-10 years, the subject of ICD deactivation has been highlighted more frequently. This could have contributed to a higher awareness among physicians in Cardiology.

Location of death

The majority of patients in study I and study II as well as 53% of all 464 ICD patients who died during 2014 (group 2) died in hospital. This confirms the results of earlier studies that it is common for ICD patients to be admitted to hospital before death [73, 74]. Many of the hospitals in our studies were university hospitals. This did not affect therapy deactivation per se; in study II more than half of the patients having therapy still active at death were inpatients in an university hospital. Those patients were most commonly treated in Cardiology wards. DNR patients under university Cardiology care who had high cardiac competence still had active devices when they died. Comfortingly though, in study IV we showed an increase in deactivation rates for DNR patients treated in Cardiology. Hopefully this will be true also for patients treated in Non-Cardiology wards when guidelines have been implemented in clinical practice. All healthcare professionals involved in the care of patients with ICD are obligated to identify key medical issues, including unnecessary ICD therapy at end of life, and to support each patient at his or her request in order to save terminally ill patients from unnecessary discomfort.

ICD knowledge

Overall, basic ICD knowledge among physicians was low, only 41% in study III reached the predefined criteria for sufficient level of knowledge to manage patients with ICD. Though physicians in Cardiology scored highest, one-third of them still did not reach a sufficient level. This result implies a need for further educational efforts. The most significant knowledge gaps existed however among physicians in Internal Medicine and Geriatrics, in line with earlier results [51., 129]. With the increasing number of ICD patients and majority of these patients treated in Non-Cardiology wards, the cardiologist will no longer be able to follow each patient. This may well shift much responsibility to primary care physicians who will then be obligated to understand fundamental technical features of these devices. Study III shows that sufficient ICD knowledge was only achieved for less than one-third of the physicians in Internal Medicine and less than one-fifth in Geriatrics. The vast majority of all respondents in study III said they had experience treating ICD patients, confirming the results from study II and study IV that ICD patients are admitted to a variety of wards.

In the patients' medical records, two abbreviations, CRT-D and ICD, are commonly used to identify that a patient has a defibrillator implanted. The results in study III showed that many physicians fail to identify these abbreviations, which could lead to misconceptions and possibly to an inability to identify that a patient has an ICD. The recently introduced S-ICD adds to the list of abbreviations physicians needs to know. Possibly it would have been easier if all the abbreviations contained a varying supplemental abbreviation to indicate specific treatment, for example ICD, ICD-CRT and ICD-S.

Physical contact with a patient during shock is not associated with any danger [20]. This is a fact of which one-third of the physicians in Geriatrics and one-fifth of the physicians in Internal Medicine in study III were unaware. This could result in resistance to comfort patients during shock therapy. Even worse, the misconception could result in the possibility of a physician not performing adequate CPR on ICD patients.

The need for external defibrillation is low, but such defibrillation can be essential if the ICD fails to convert an arrhythmia. Almost one-third of all physicians falsely stated that one can not externally defibrillate a pulseless ICD patient, and 40% said they did not know how to handle an ICD patient with cardiac arrest. This may potentially result in delayed or possibly inadequate treatment. Comfortingly though, almost all of the attending physicians within Cardiology said they knew how to handle SCA in ICD patients.

Some physicians are not aware of the ICD function when it is deactivated. In study III, over one-third of physicians' working in Non-Cardiology departments thought deactivation of shock therapy in an ICD weren't possible. Furthermore, one-third of all physicians' thought that deactivation would also turn off the pacing function regardless of the method used i.e. programmer or magnet application. This can lead to reluctance to perform therapy deactivation in patients at end of life thus exposing them to an unnecessary risk of shocks.

Guideline compliance

ICD treatment prevents SCD and improves total survival both in secondary prevention as well as in primary prevention populations [36]. Only half of the physicians in study III knew both indications. When physicians were asked about their awareness about international guidelines, seventy-seven percent of all physicians and 38% in Cardiology, said they had little or no knowledge of them, confirming earlier data that showed a low awareness of ICD guidelines, particularly in physicians working outside Cardiology [45, 46, 48, 50].

The national guidelines from the National Board of Health and Welfare in Sweden have in 2015 highlighted the question regarding deactivation in ICD patients at end of life [13]. International guidelines emphasize that advanced care planning should include deactivation of ICD therapy [76, 81, 130]. Furthermore, it has been shown that if hospitals have an ICD deactivation policy the rate of ICD deactivation may increase [91].

7 CONCLUSIONS

- More than one-third of patients had a ventricular tachyarrhythmia within the last hour of life, 31% received shock treatment and 24% had an arrhythmic storm during the last 24 hours of life.
- In ICD patients cardiac death was the primary cause and heart failure the specific cause of death in the majority of cases while an arrhythmic cause was found in 13%.
- The ICD remained active in half of the patients with a DNR order; almost one-fourth of these patients received one or more shocks in the last 24 hours of life.
- ICD patients with a DNR order and active shock treatment had a median of four days or more between DNR decision and death.
- For more than one-third of patients with ICD therapy deactivated two days or more elapsed between DNR decision and decativation.
- Device malfunction was found in 3% of cases and was mainly attributable to undersensing of ventricular fibrillation.
- Most ICD patients died in hospitals, many in university hospitals. Two-thirds of those patients were treated in Non-Cardiology departments before death and only one-third of them were treated in Cardiology.
- Test scores revealed insufficient knowledge of ICD therapy in the majority of participating physicians, that possibly could affect their ability to manage ICD patients. Physicians rate their knowledge to be low although many had earlier experience in treating patients with ICD.
- The increase in therapy deactivation in ICD patients with DNR since publication of guidelines on ICD management at end of life is statistically significant for patients treated in Cardiology wards.
- With an increasing ICD population there is an urgent call for actions to bridge the knowledge gap between the guidelines' recommendations and clinical practice.

8 CLINICAL IMPLICATIONS

- An increased knowledge of the incidence of ventricular tachyarrhythmia and shock treatment at the end of life for patients with ICD may lead to improved care and a lower incidence of unnecessary and painful shocks for patients close to death.
- When a ICD patients health status detoriates significantly and a decision is made not to resusitate (DNR), it is imperative to discuss deactivation of the device. Highligtning the question of deactivation among physicians, nurses and patients may increase the number of future deactivations.
- All physician involved with ICD patients have to understand fundamental technical features of these devices and the managment at end of life to be able to deliver best possible care for this exposed group of patients.

9 FUTURE PERSPECTIVES

- Discussion about end of life care in ICD patients has to be done more systematically; could a palliative consultations be a of any help for patients and healthcare proffessionals?
- Systematically post-mortem interrogation of devices can help institutions to improve the quality of patient care.
- Decreasing number of inappropriate shocks may have an influence on patient QOL and possibly decreasing anxiety and depression levels. Future studies may reveal this.
- Home monitoring system and deactivation – is this the way forward – can it be done safe and secure?
- The awareness of ICD guidelines and clinical management has to increase and disseminate knowledge beyond Cardiology.

10 SVENSK SAMMANFATTNING

Inledning

Patienter med hög risk att drabbas av livshotande rytmrubbningar kan i förebyggande syfte få en implanterbar defibrillator (ICD) inopererad. Defibrillatorn bryter hjärtrusningar med chocker eller sekvenser av snabba pacemaker-stimuleringar. Indikationen för ICD behandling är antingen att personen har överlevt ett hjärtstopp eller en livshotande kammartakykardi, s.k. sekundärprofylax, alternativt har en ökad risk för livshotande rytmrubbningar på grund av en nedsatt hjärtfunktion s.k. primärprofylax. I ett flertal studier har man kunnat visa en förbättrad överlevnad både i sekundär så väl som primär profylaktisk ICD behandling. Antalet patienter med ICD behandling ökar i hela världen och även i Sverige. Under 2014 fanns det drygt 9000 patienter med aktiv behandling. Socialstyrelsens riktlinjer har höjt prioriteringen för ICD behandling vilket bidragit till den ökade implantationsfrekvens. Läkare som vårdar patienter med ICD måste känna till behandlingen för att kunna ge bästa möjliga vård. Även om ICD skyddar mot plötslig död kommer vi alla att så småningom avlida av ålderdom eller av underliggande sjukdom. Under 2010 publicerade internationella riktlinjer för att belysa och lyfta frågor som rör vården av patienter med ICD i livets slutskede. Det saknas djupare kunskap om vad som händer i samband med att dessa patienter avlider. Det övergripande syftet med denna avhandling var att studera patienter med ICD i livets slutskede samt att undersöka läkares kunskapsnivå avseende ICD behandling och följsamhet till riktlinjer gällande patienter med ICD i livets slutskede.

Metod och Resultat:

Studie I: är en observations studie där explanterade ICD dosor från 125 avlidna patienter undersöktes. Syftet var att studera ICD dosor för att få en ökad kunskap om kammararytmier, chockterapi och eventuella tekniska fel i samband med att patienter med ICD avlider. Resultatet visade att 71% av patienter med ICD dör på sjukhus, vanligen pga. hjärtsvikt. Det var 35% av patienterna som hade någon form av kammararytmi sista timmen i livet och 31% fick chock behandling under de sista 24 timmarna. Det var mer än hälften (52%) av patienterna i studien som hade en s.k. behandlingsbegränsning och där vården övergått till palliation. Trots det så var det 51% som fortfarande hade chockterapierna aktiva när de dog. Nästan en fjärdedel fick chock som en konsekvens av detta.

Studie II: är en observationsstudie där de 65 patienter med beslut om behandlingsbegränsning från studie I ingår. Syftet var att kartlägga hur patienter med behandlingsbegränsning och ICD vårdas, var de behandlas när de dör, samt durationen mellan behandlingsbegränsning och deaktivering av chockterapier. Resultaten visar att

majoriteten (86%) av patienterna dör på sjukhus. Av dessa så vårdas 63% på universitetets sjukhus och 33% på hjärtavdelningar. Trots behandlingsbegränsning var ICD chock aktiv hos 51% av patienterna och 24% fick chock terapier under sista dygnet. Tiden från beslut om behandlingsbegränsning och död hos patienter med terapier aktiva var 4 dagar (IQR 1-38). Hos dem med terapier avstängda, så tog det 2 dagar eller mer mellan beslut om behandlingsbegränsning och deaktivering för mer än en tredjedel (38%) av patienterna.

Studie III: är en deskriptiv tvärsnitts studie. En enkät utarbetades i forskargruppen och delats ut till läkare verksamma inom kardiologi, internmedicin samt geriatrik på slumpmässigt utvalda sjukhus i Sverige. För att nå tillräcklig kunskapsnivå var respondenten tvungen att svar rätt på sju av nio viktade kunskapsfrågor. Syftet att kartlägga och jämföra kunskapsnivån gällande ICD behandling i allmänhet samt i livets slutskede, hos kliniskt verksamma läkare inom kardiologi, internmedicin och geriatrik. Resultatet visade att många (83%) av läkarna hade tidigare erfarenhet av att vårda patienter med ICD men att 68% ansåg att deras kunskapsnivå gällande ICD behandling var låg. Totalt erhöll 41% av läkarna resultatet tillräcklig kunskap. Läkare inom kardiologi hade signifikant högre resultat än läkare från de andra specialiteterna. Endast 30% av läkare inom internmedicin och 19% av dem inom geriatrik som nådde nivån tillräcklig kunskap jämfört med 71% inom kardiologi.

Studie IV: är en observationsstudie, där två grupper av patienter med ICD som avlidit på sjukhus före och efter publicering av internationella riktlinjer jämförs. Grupp 1 bestod av 89 patienter från studie I, alla avled på sjukhus under 2010 eller tidigare. Under 2014 avled total 464 patienter med ICD i Sverige. Av dessa dog 253 patienter på sjukhus och 246 av dem inkluderades i grupp 2. Ett sjukhus, av totalt 63, med sju patienter beslöt sig för att inte delta i studien. Syftet var att undersöka om förekomsten av deaktivering av chock terapier har ökat efter publicering av nya riktlinjer gällande patienter med ICD i livets slutskede. Resultatet visade att två tredjedelar av patienter med ICD vårdas på på andra avdelningar än kardiologen när de dör. Beslut om behandlingsbegränsningar är vanligt, för grupp 1 54% och 73% för grupp 2. Deaktivering av chock ökade från 52% för grupp 1 till 67% för grupp 2. Denna ökning var dock enbart signifikant ($p< 0.016$) för de patienter med behandlingsbegränsning och som vårdades på kardiologen. En signifikant skillnad ($p= 0.038$) fanns även inom grupp 2 för de patienter med behandlingsbegränsning, chocker deaktiverade och som vårdats på kardiologen jämfört med de som vårdats på andra avdelningar. Tiden mellan beslut om behandlingsbegränsning och deaktivering var två dygn för omkring 40% av patienterna i båda grupperna.

Slutsats

Patienter med ICD i livets slutskede vårdas på sjukhus i samband med att de dör och två tredjedelar vårdas på icke kardiologiska avdelningar. ICD patienter har kammararytmier i samband med att de dör. Många av patienterna har en behandlingsbegränsning, men trots det är chockterapier fortfarande påslagna hos en stor andel av patienterna och många riskerar därför onödiga chocker som en konsekvens av aktiva terapier. Andelen patienter som får sina terapier deaktiverade har ökat men inte signifikant sedan publicering av nya internationella riktlinjer gällande patienter med ICD i livets slutskede. Många läkare har inte tillräckliga kunskaper om ICD behandling. Kunskapen är låg framförallt hos läkare som arbetar utanför kardiologi, men även inom kardiologen behöver kunskapsnivån höjas för att höja kvaliteten och säkerställa en bra vård i livets slutskede för patienter med ICD.

11 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all of you who have supported me and helped me though with the work during my doctoral studies and made this thesis possible.

First of all I would like to express my sincere gratitude to all participating hospital throughout all studies an all physicians who answered the survey in study III. I sincerely hope this work will make a difference for future patients.

Viveka Frykman my principal supervisor. Thank you for all your support and help throughout the whole process, without you I would not be where I am today. Thank you for your excellent knowledge and guidance in science and research; for believing in me and for a never-ending encouragement. You have always been available for questions, discussions and difficulties that we have encounter along the way. Finally, I want to thank you for all the laughs we have had together during the hard work, makes life so much easier.

Mårten Rosenqvist, my co-supervisor, for sharing your brilliant and impressive knowledge in science and research. For sharing your experience, giving me valuable guidance and support, always quick with a response; and for being calm and telling me that in science "all news are good news" when we were up against some head wind.

Anne-Cathrine Mattiasson, my co-supervisor for support and help throughout the research process; always quick with a response and with an attention for details.

Hans Persson, my mentor, for your encouragement and always interested in how things are going. Constantly on the move but always taking the time and talk for a moment.

Karin Malmqvist, Head of the Department of Cardiology, for your great interest and support and for making clinical research possible for me and all fellow researchers in this eminent department.

Andreas Kling and **Birgitta Åslund**, Manager and Head nurse, for your flexibility and positive attitude towards my research, despite the problems it sometimes has caused in the clinical work. I know the fight with my research time in Heroma has not been an easy task to deal with.

Johanna Sjöblom, co-author, colleague and friend, for all your help, support and for all interesting discussions during the years. It has been great to work with you through our studies and to have had your company during all our courses. It was really great to do this journey together.

Richard Sutton, co-author, former supervisor, for your help with study I and II, and for introducing me to research in the early beginning and for always being very kind.

Jackline Magnsjö, co-author, colleague and friend, for you tireless work with study I, II and IV. It has been invaluable. Without your help it would have taken me twice as long.

The management and administrative staff at the Department of Clinical Science**,** Karolinska Institutet Danderyds Hospital. For your support and help throughout the years; **Håkan Wallén** for your help and encouragement and **Nina Ringart** for all your assistance with my questions and travels, and for always being quick with a response. **Fredrik Johansson,** statistician at KI DS, for your support, help and patience.

Boel, Carolin, Charlotta, Eva, Jackline, Marie, Pia, Suzanne colleagues and friends at the Arrhythmia clinic, you have all been of great support, contributing with your expertise and help me throughout all these years. I know you have been working extra hard sometimes to make this happen, I will always be thankful to you all for that.

Carolin Nymark, colleague and friend, finally the goal is achieved for us both. I am grateful to have had you along on this journey, your support, advice and not the least all laughs we have had, it has been very valuable to me.

Eva Qvarnström, colleague and friend, for your support and for interesting discussions regarding the electricity of it all, and for your collaboration before, during and after the exams - it had not been possible without you.

Hans Erntell, colleague and friend, for your great expertise and help during all studies and particular study III. You always make time to engage in discussions, have been very supportive and also for all our laughs.

Raffaele Scorza colleague and friend, for your great expertise and help during all studies but particular with study I, and for all your support during the exams.

Josephine Muhrbeck, colleague**,** for valuable language help.

To all other **colleagues and friends** at the Arrhythmia Clinic and the Department of Cardiology for supporting me over the years and contributing to a great atmosphere.

To all the staff in the **Pathology department** at Danderyd Sjukus for your assistance in the early face of study I.

John Martin Corander for your working during last summer, helping me with data in study III.

Johan Adelgren, photographer at Danderyds Sjukhus, for helping me with pictures, figures and tables.

Fred Saboonchi, psychologist, for your great expertise in the field of psychometrics.

To all the staff at the medical library at Danderyd Hospital, especially **Love Strandberg** for your help with references, copyright question and all other format issues.

Fredrik Gadler and **Anita Fredensson**, for all your work and contributing with data from the **Swedish ICD and Pacemaker Registry**.

All **fellow physicians in the Cardiology** department and the **physicians from Internal Medicine** and **Geriatrics** department at Danderyds Hospital for participating in focus groups and helping out with the construction of the questionnaire for study III.

Jenny Findahl, graphic designer and old friend, thank you for the beautifully cover of this book, assistance with pictures and tables during the years and for being a great friend.

Siv-Britt Kinch, my mother, for always encouraging me to study and to pursue with academic work, for being a great mum and a great mormor to my kids. Always close when I need to talk and always supportive. Thank you for helping us with the kids throughout this work.

Marianne Westerdahl, grandmother and mother in law, Thank you for your illustration. Most of all thank you for helping us with the kids during all these years, making it possible to study. Thank you for being the best svärmor and farmor ever.

Claes, my beloved husband and best friend, thank you for your support and encouragement during all these years. Thank you for all your help with confusing p, binominal distributions and power. You have always believed in me and being supportive and for making me challenge myself to do things in life I have not yet tried, Thanks!

Thea, Clara och Tobias – mina älskade barn. Nu är det klart! Tack för att ni hållit mig i handen under dessa år och för att ni hållit mig kvar på jorden och för all er kärlek.

I would like to express my gratitude to the funders. This research project has received from: Mats Kleberg Foundation, Laerdal Foundation, Ragnhild and Einar Lundströms Remembrance Foundation, Boston Scientific, Medtronic Inc, Fond 176 Danderyds Hospital, Vårdpersonal Inom Kardiologi.

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